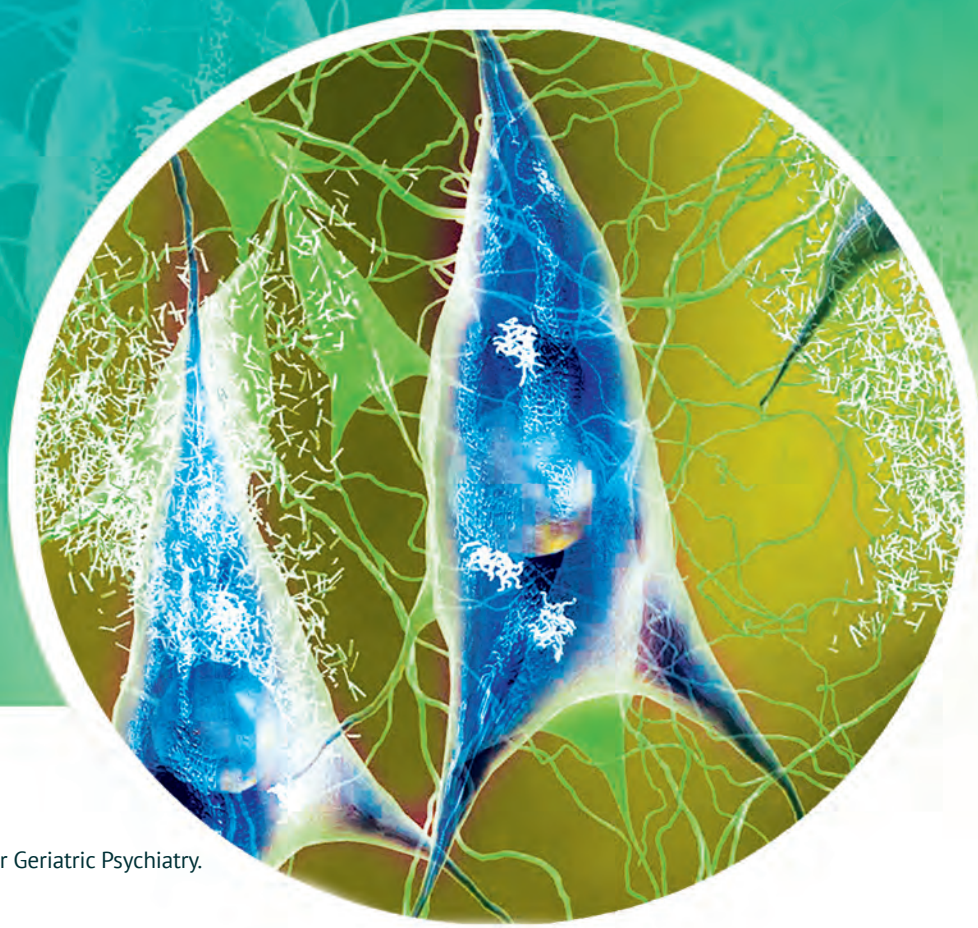
ALZHEIMER'S DISEASE 2017:

Early Diagnosis and Multifactorial Management Towards a New Therapeutic Window and a Disease Modifying Approach

SATURDAY, MARCH 25, 2017



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AAGP American Association for Geriatric Psychiatry

Provided by Med Learning Group and the American Association for Geriatric Psychiatry.
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Alzheimer's Disease 2017: Early Diagnosis and Multifactorial Management Towards a New Therapeutic Window and a Disease-Modifying Approach

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Program overview

This live activity is focused on the imaging techniques in the study of Alzheimer's disease, related disorders, and normal aging.

Target Audience

This activity is designed to meet the educational needs of clinicians involved in the diagnosis and care of individuals with memory or other cognitive complaints, including geriatricians, geriatric psychiatrists, neurologists, radiologists, and neuropsychologists

Learning Objectives

After completing the CME activity, learners should be better able to:

- Discuss how clinical, cognitive and neuroimaging tests should be integrated to achieve an early and accurate diagnosis of Alzheimer's Disease (AD)
- Apply evidence on currently available treatments and their optimization across the spectrum of AD
- Review therapeutic targets and emerging data on investigational agents that support early treatment and a new disease-modifying approach to delay or slow AD progression

Credit Designation

The American Association for Geriatric Psychiatry (AAGP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The American Association for Geriatric Psychiatry designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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- Dr. Marc Agronin is on the speakers' bureau for Allergan.
- Dr. Bradford Dickerson is a consultant for Merck, Lilly, and Biogen. He receives royalties from Oxford University Press and Cambridge University Press.

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This activity is facilitated by Med Learning Group.

Provided by the American Association for Geriatric Psychiatry

Supported by an Educational Grant from Eli Lilly and Company

Program Agenda:

I. Alzheimer's Disease: Disease State Overview and Unmet Clinical Needs
   A. Disease Pathophysiology and Models
      3D video of Disease Pathophysiology

II. Diagnosis of Alzheimer's Disease: Integration of Clinical and Biomarkers Assessment
   A. Diagnostic Techniques (MRI, FDG PET, Amyloid PET, CSF Tau/Aβ42, Tau-PET)
   B. Updates in Guidelines for Diagnostic Criteria (2011)
   C. Review of biomarkers' trajectories in the progression of Alzheimer's Disease
   D. Importance of early diagnosis and challenges encountered in obtaining an early and accurate diagnosis of cognitive impairment
      - 2/3 Case studies on AD differential diagnosis as established with the integration of biomarkers and clinical evaluation

III. Evolving Role of Amyloid Imaging in the Diagnosis of AD
   A. Amyloid radiotracers and emerging Tau Imaging
   B. ApoE, age and risk of progression to AD
   C. Appropriate and inappropriate use of amyloid-PET: guidelines and use in the clinic

IV. Emerging Data on Disease Modifying Therapies as a New Therapeutic Approach to AD
   A. Overview of current standard of care and unmet needs
   B. Anti-amyloid monoclonal antibodies: rationale and development
      3D video of the mechanism of action of anti-amyloid agents (solanezumab)
   C. Phase 3 data of bapineuzumab and solanezumab; an update.
   D. Other anti-amyloid monoclonal in development: aducanumab and crenezumab
   E. Prevention trials
   F. Other investigational approaches

VI. Conclusions

VII. Questions and Answers

VIII. Adjournment

AAGP Symposium ~ March 25, 2017 ~ Dallas, TX

Alzheimer's Disease 2017: Early Diagnosis and Multifactorial Management Towards a New Therapeutic Window and a Disease-Modifying Approach

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Learning Objectives

- Discuss how clinical, cognitive and neuroimaging tests should be integrated to achieve an early and accurate diagnosis of Alzheimer's Disease (AD)
- Apply evidence on currently available treatments and their optimization across the spectrum of AD
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Alzheimer's Disease: Amyloid and Beyond

Bradford C. Dickerson, MD

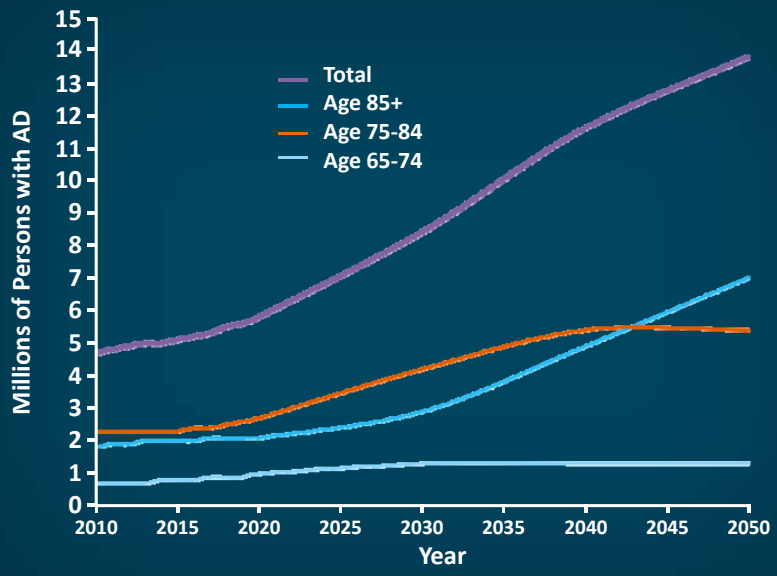
Updated to 2017

The Scope of Alzheimer's Disease (AD)

- AD is the most common form of dementia and accounts for 60% to 80% of all cases.[1]
- AD afflicts more than 5 million individuals in the US, with a projected increase to almost 16 million by 2050.[1,2]
- Dementia affected 46.8 million people worldwide in 2015. This number will almost double every 20 years, reaching 131.5 million in 2050.[3]

1 Alzheimer's Association, 2017. (www.alz.org/facts/downloads/facts_figures_2017.pdf). 2. Hebert LE et al. *Neurology*. 2013;80:1778-1783. 3. Alzheimer's Disease International, 2015. (https://www.alz.co.uk/research/world-report-2015).

The Aging Population and the AD Epidemic

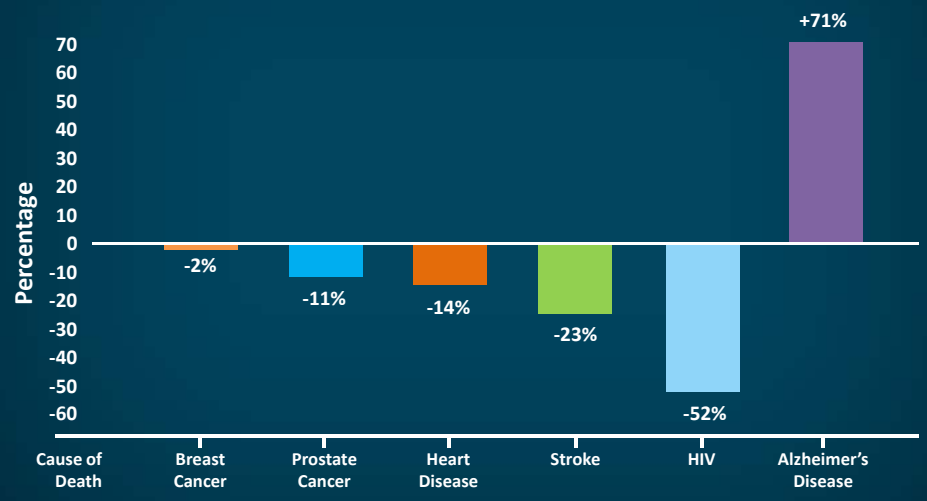


After age 65, the prevalence rate of AD doubles every 5 years, from <5% at age 65 to nearly 50% of individuals 85 years and older.[1]

Hebert LE, et al. *Neurology.* 2013;80:1778-1783.

Alzheimer's Deaths Continue to Increase; Deaths from Other Major Diseases Decrease

Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2013



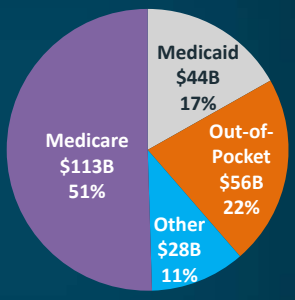
Xu JQ, et al. National Center for Health Statistics. 2016. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf. Accessed November 1, 2016. Alzheimer's Association, 2016. (www.alz.org/facts/downloads/facts_figures_2016.pdf)

Updated to 2017

Social and Economic Costs of AD

- AD is the sixth leading cause of death in the US.[1]
- In 2017, Alzheimer's and other dementias will cost the nation $259 billion[1]
- Annual costs for health care for patients with AD and other dementias are expected to increase to more than $1.1 trillion in 2050.[1]
- In 2015, the total annual per-person healthcare and long-term care payments in the US was more than three times the costs for someone without AD.[1]

2017 Costs of Alzheimer's* = $259 Billion (B)



Total does not add due to rounding
*Data are in 2017 dollars.

- AD appears to be the most costly illness in the United States, even more so than cancer and heart disease.[2]

Alzheimer's Association, 2017 (www.alz.org/facts/downloads/facts_figures_2017.pdf). 2. Hurd MD et al. N Engl J Med. 2013;368:1326-1334.

The Problem With Delayed Diagnosis

- It takes, on average, up to 2 years for an individual with symptoms to see a physician and up to 1 year to get a diagnosis.[1, 2]
- It is estimated that 20% of those individuals in the US who have AD are never clinically diagnosed![3]
- This is true despite the facts that many obvious benefits to early diagnosis exist and effective pharmacological treatments for the symptoms of AD have been on the market for over 15 years.

1. Balasa M et al. *Neurology.* 2011;76:1720-1725. 2. Boise L et al. *Gerontologist.* 1999;39:457-464. 3. Mok W et al. *Am J Alzheimer's Dis Other Demen.* 2004;19:161-165.

Diagnostic Criteria in AD

Bradford C. Dickerson, MD

Diagnostic Criteria for AD

- In 1984, the first diagnostic criteria for AD were developed by NINCDS and ADRDA of the Alzheimer's Association, commonly referred to as NINCDS-ADRDA criteria.[1]
- NINCDS-ADRDA and the American Psychiatric Association (APA) DSM-4-TR criteria were, until recently, the most commonly used guidelines.
- In 2013, DSM-5 changed the term "dementia," which was used in DSM-4-TR, to "neurocognitive disorder" (NCD) and included AD as a subtype of this general term.[2,3]

NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; ADRDA = Alzheimer's Disease and Related Disorders Association; DSM = *Diagnostic and Statistical Manual of Mental Disorders.*

1. McKhann G et al. *Neurology.* 1984;37:939-944. 2. APA. DSM-4-TR. Washington, DC: American Psychiatric Association; 2000. 3. APA. DSM-5. Arlington, VA: American Psychiatric Association; 2013.

A Change in Terminology . . .

"Dementia" has been replaced by "**major neurocognitive disorder**" in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders,* or *DSM-5*.

A major neurocognitive disorder is defined by evidence of significant cognitive decline from a previous level of performance that interferes with independence in everyday activities, based on individual, informant, and/or test data, and that is not accounted for by delirium or another mental disorder in one or more of the following cognition domains: complex attention, executive function, learning and memory, language, perceptual-motor, and social cognition.

APA. DSM-V. Arlington, VA: American Psychiatric Association; 2013.

Neurocognitive Disorders in DSM-5: Impairment Across 6 Key Domains

Domain	Symptoms
Complex attention	Ability to attend to and process multiple stimuli
Executive function	Ability to plan, organize, and complete tasks/projects
Learning and memory	Acquiring, manipulating, and remembering items, facts, words and their meanings, events, people, procedures, skills, etc.
Perceptual-motor	Identification and manipulation of figures, maps and items; motor tasks; recognition of faces and colors
Language	Expressive and receptive language skills
Social cognition	Socially appropriate behaviors and decision-making; empathy

APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

Syndromal Definitions: DSM-5

- **Mild neurocognitive disorder (eg, MCI/prodromal AD)**
  - Mild cognitive decline (preferably by neurocognitive testing or, in its absence, other quantified clinical testing)
  - Does not interfere with independence
  - Not due to delirium
  - Not attributed to another mental disorder (eg, major depression, schizophrenia)
- **Major neurocognitive disorder (dementia, eg, due to AD)**
  - Major cognitive decline (preferably by neurocognitive testing or, in its absence, other quantified clinical testing)
  - Interferes with independence
  - Not due to delirium
  - Not attributed to another mental disorder (eg, major depression, schizophrenia)

APA. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

The Spectrum of NCDs

- Alzheimer's disease
- Vascular dementia
  - Cortical
  - Subcortical
- Frontotemporal
  - Behavioral variant
  - Semantic dementia
  - Progressive aphasia
  - Progressive supranuclear palsy
  - Corticobasal degeneration
- Dementia with Lewy bodies
- Medical
  - Neoplasm
  - Trauma/anoxia
  - NPH
  - Toxins
  - Infections
  - Neurologic illness
  - Organ failure

NPH = normal-pressure hydrocephalus .

Diagnostic Criteria for AD (NIA-AA and IWG)

- **AD dementia**
  - Cognitive impairment
  - Impairment of activities of daily living
  - Biomarker evidence of AD
- **Prodromal AD (MCI of the AD type)**
  - Amnestic or non-amnestic cognitive impairment
  - No or minor impairment of activities of daily living
  - Biomarker evidence of AD
- **AD at-risk state (preclinical AD)**
  - No cognitive impairment on testing (possible subjective impairment)
  - No functional impairment
  - Biomarker evidence of AD

IWG = International Work Group.

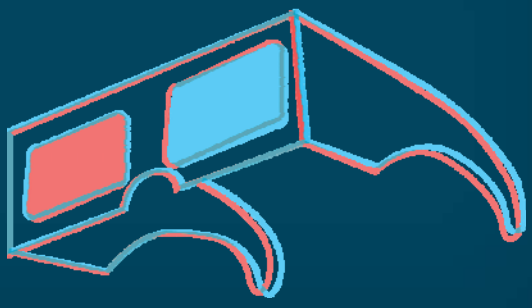
Dubois B et al. *Lancet Neurol.* 2007;6:734-746. Dubois B et al. *Lancet Neurol.* 2010;9:1118-1127. McKhann GM et al. *Alzheimers Dement.* 2011;7:263-269. Albert MS et al. *Alzheimers Dement.* 2011;7:270-279. Sperling RA et al. *Alzheimers Dement.* 2011;7:280-292.

Alzheimer's Disease Risk Factors

AD less likely
Education
Exercise
Brain fitness
Antioxidant diet
Heart health
Social activity

AD more likely
Age
Female gender
APOE ε4 genotype
(other genes: early vs. late)
Hypertension
Diabetes
Homocysteine
Cholesterol
Head trauma
Family history

Please put on your 3D glasses



3D Video

Pathophysiology of Alzheimer's Disease

Review of Biomarker Changes in AD Progression

Bradford C. Dickerson, MD

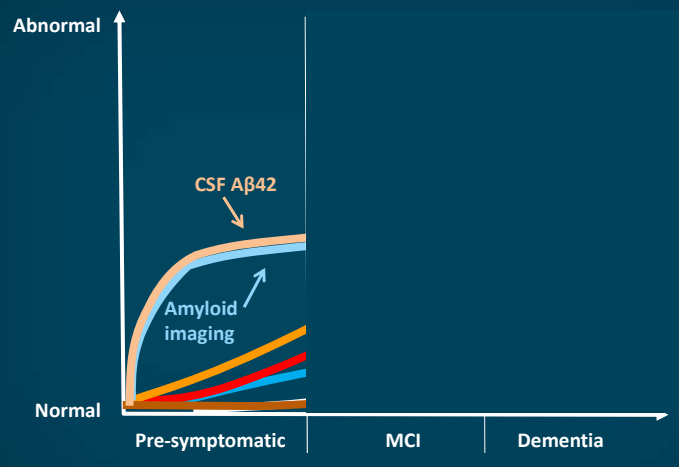
Biomarkers for Alzheimer's Disease

Biomarker Measurement	Biomarker Changes Consistent with Alzheimer's Disease
$A\beta_{42}$ accumulation[1,2]	$A\beta_{42}$ levels decrease in CSF. $A\beta_{42}$ can be seen in amyloid-based PET scan.
TAU_{HP} accumulation[3]	TAU_{HP} levels increase in CSF.
Synaptic dysfunction[4]	Hypometabolism seen on FDG-PET.
Loss of brain volume[5]	Atrophy is seen on MRI and can be measured with MRI volumetrics.

FDG = fluorodeoxyglucose.

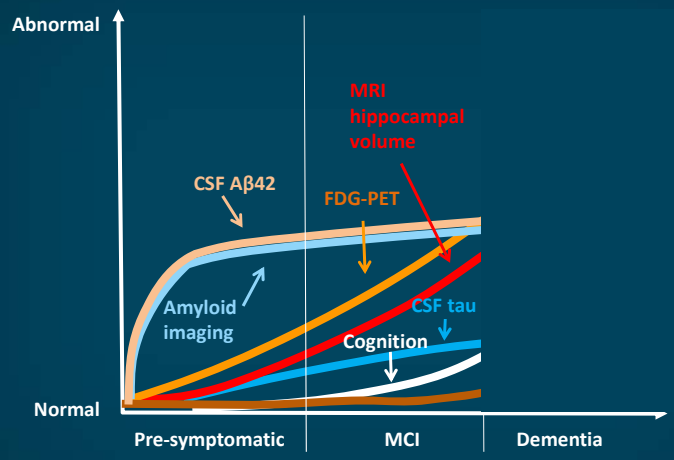
1. Sperling RA et al. *Neuron.* 2009;63:178-188. 2. Morris JC et al. *Arch Neurol.* 2009;66:1469-1475. 3. Fagan AM et al. *Arch Neurol.* 2007;64:343-349.
4. de Leon MJ et al. *AJNR Am J Neuroradiol.* 1983;4:568-571. 5. Atiya M et al. *Alzheimer Dis Assoc Disord.* 2003;17:177-195.

Biomarker Changes During AD Progression



Jack CR Jr, et al. *Lancet Neurol.* 2010;9:119-28.

Biomarker Changes During AD Progression



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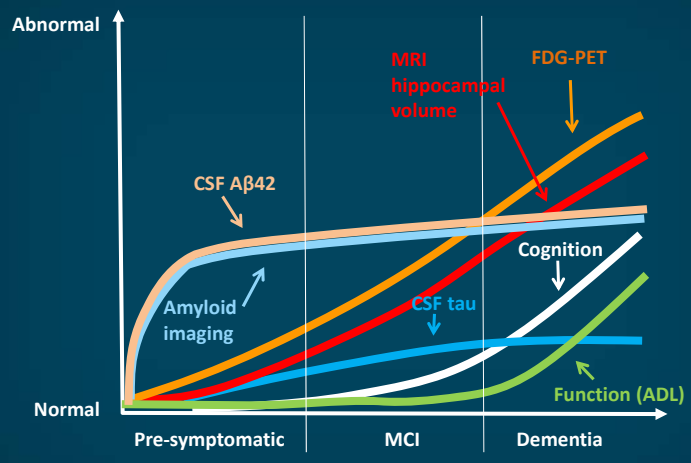


Jack CR Jr, et al. *Lancet Neurol.* 2010;9:119-28.

Overall Approach To and Goals of Evaluation

- **The clinical illness**
  - What is the patient's overall dementia clinical status?
    - Subjective cognitive concern, MCI, dementia (& dementia stage)
  - Is there a recognizable clinical syndrome?
    - Amnesic and dysexecutive dementia, aphasic MCI, etc.
  - Are there important accompanying clinical features?
    - Motor features, psychiatric symptoms
- **The neurobiological disease**
  - What laboratory, imaging, or other biomarker evidence do we have for the specific brain disease?
- **How can we use all of this information to develop a comprehensive treatment and care plan?**

Case Study 1 - Presentation

- 66 year-old man with 2 years of gradually progressive impairment in:
  - episodic memory (forgetting important information from recent experiences, including conversations at work and at home, with repetitive asking of questions),
  - judgment and problem solving (had new, uncharacteristic difficulty with tax preparation), with no reported language, visual, motor, or mood/behavioral symptoms.
- His impairments resulted in the increasing need for his assistant's help at work, and his wife had to help with the taxes. Medical and family history were unremarkable except for mild hypertension.
- He also reported symptoms consistent with active major depressive disorder, of mild severity.

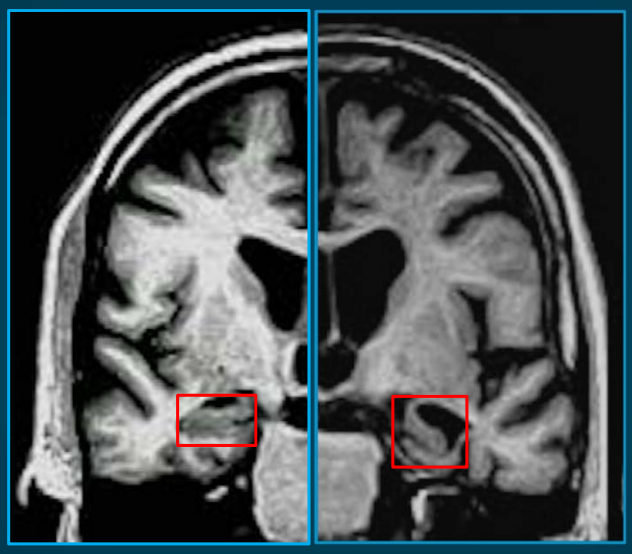
Case Study 1 - Exam

- Impaired episodic memory acquisition, retention and retrieval, impaired complex attention and executive function, otherwise normal.
- Neurological exam was normal.
- Montreal Cognitive Assessment (MoCA): 25 (-4 for memory, -1 for verbal fluency).
- Mini Mental State Exam: 27 (-3 for memory)
- GDS 11

Case Study 1

- **Brain MRI**: symmetrical atrophy in bilateral rostral hippocampal and medial temporal cortex, medial and lateral parietal cortex, and posterior lateral temporal cortex.
- **Neuropsychological testing**: verbal storage and retrieval impairment (<1 percentile), and impaired executive function (<5 percentile); otherwise normal performance.

MRI: Hippocampal Atrophy in AD



Normal AD

Case Study 1 – Question 1

- What would be the diagnosis at this point?

A. Dementia of unknown etiology

B. MCI, possibly due to AD

C. MCI, possibly due to depression

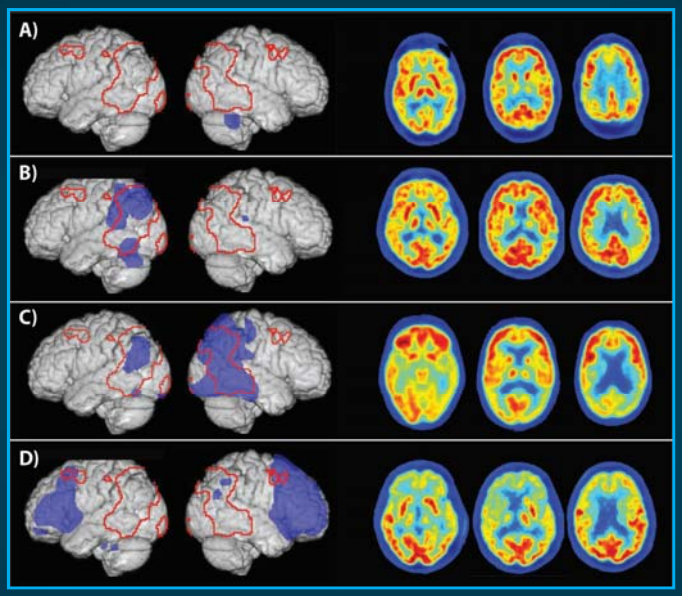
D. More than one of the above

- A diagnosis was made of mild cognitive impairment, multidomain amnesia-predominant syndrome with executive dysfunction, likely early pre-dementia stage AD; the clinician wanted additional information to support this concern

Case Study 1 – Additional Biomarkers

- **An FDG-PET** was obtained which showed bilateral inferior parietal, posterior cingulate, and posterior temporal hypometabolism.
- **CSF profile of Aβ and tau** proteins was highly consistent with underlying AD pathology.
- As part of a research study, an **amyloid PET** scan was visually read as positive.
- These biomarkers brought diagnostic confidence in suspected etiology to 99%. The final clinical diagnosis was:
  MCI, amnesia-predominant multi-domain syndrome, highly likely due to AD pathology, with comorbid depression.

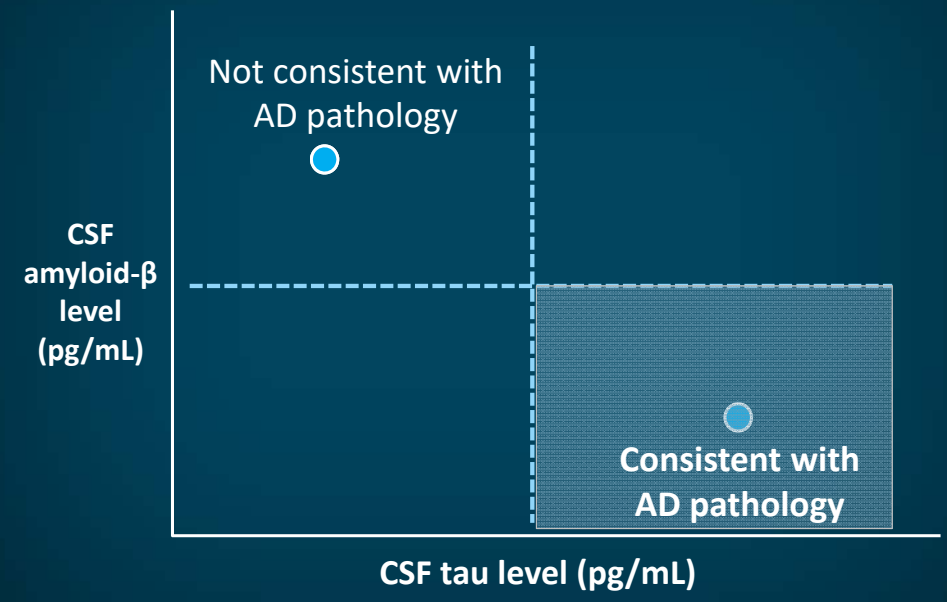
FDG-PET in Normal Aging, MCI, AD, and FTD



NL = normal; MCI = mild cognitive impairment; pAD = probable Alzheimer's disease; fTD = frontotemporal dementia.

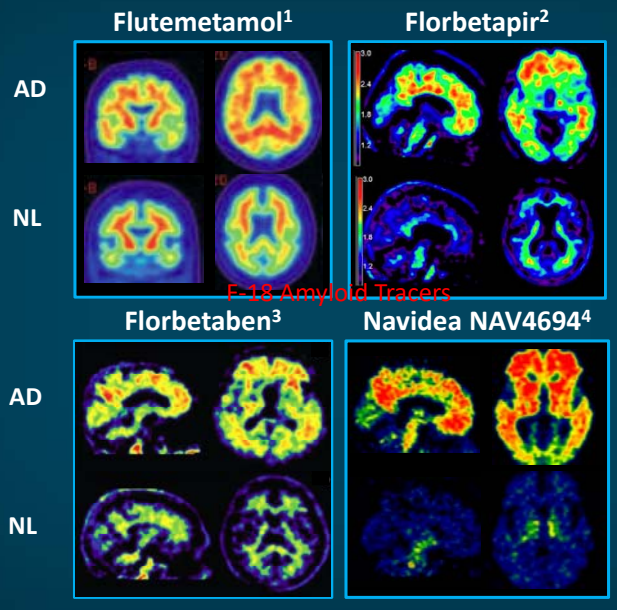
Reiman EM, et al. *N Engl J Med*. 1996;334:752-8. Reiman EM, et al. *Proc Natl Acad Sci U S A*. 2001;98:3334-9. Reiman EM, et al. *Proc Natl Acad Sci U S A*. 2004;101:284-9. Reiman EM, et al. *Proc Natl Acad Sci U S A*. 2005;102:8299-302.

CSF Markers of AD Pathology



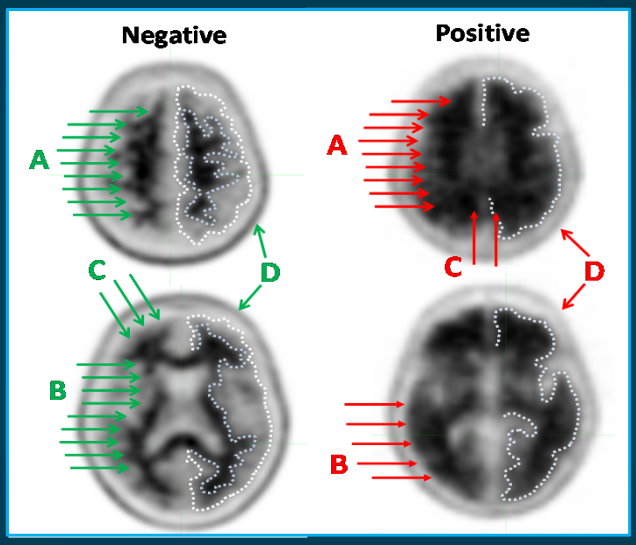
Shaw LM et al. *Ann Neurol.* 2009;65:403-413.

F18 Amyloid Imaging Tracers



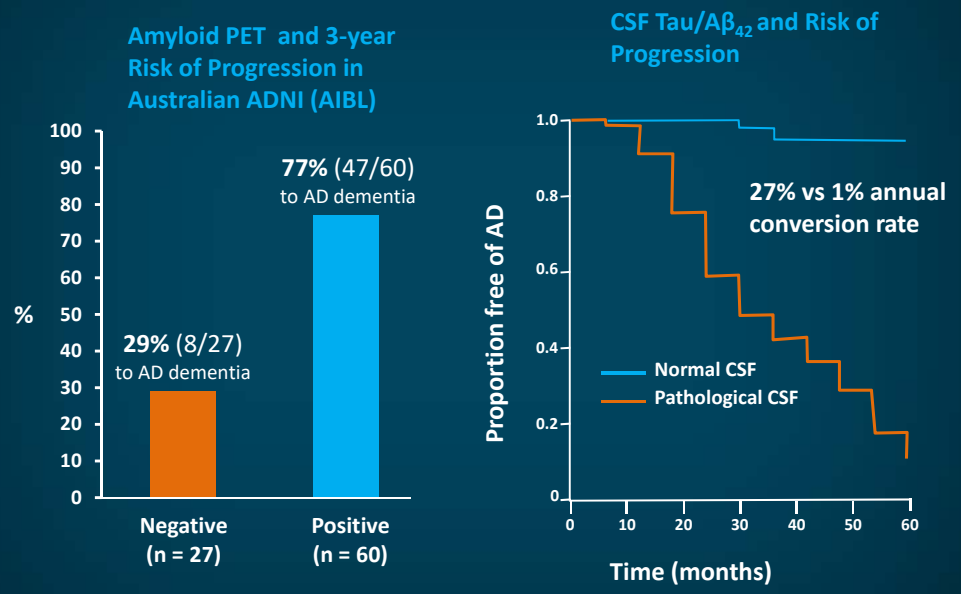
1. Vandenberghe R et al. *Ann Neurol*. 2010;68:319-329. 2. Barthel H et al. *Lancet Neurol.* 2011;10:424-435. 3. Wong DF et al. *J Nucl Med.* 2010;51:913-920. 4. Chen K et al. *Alzheimer's Dement.* 2012;8(4 suppl):P14(abstract IC-P-011).

Interpreting Amyloid PET Scans



Amyvid™ florbetapir F 18 injection prescribing information. Eli Lilly and Company, Indianapolis, IN, revised 2013. Available at http://pi.lilly.com/us/amyvid-uspi.pdf

Risk of Progression from MCI to AD



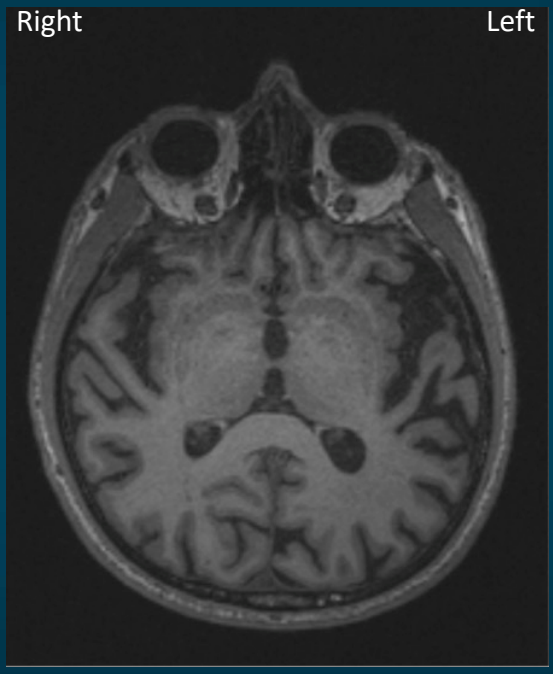
1. Rowe CC et al. *Ann Neurol*. 2013;74:905-913. 2. Hansson O et al. *Lancet Neurol*. 2006;5:228-234.

Case Study 2

- A 65 year-old right-handed woman presented with a two-year history of gradually progressive language symptoms:
  - Difficulty finding words in conversation, increasing mispronunciation of words, and new problems spelling. Intact memory, and no reported symptoms involving spatial or temporal orientation, judgment and problem solving, motor, or behavioral-psychiatric symptoms, except that she reported feeling mildly depressed.
  - Retired at 60; actively volunteering for 20 hours each week at her local library with little difficulty, and was otherwise functioning independently, living by herself. Medical and family history were unremarkable.
  - Exam: Speech was articulate and fluent at times but with word retrieval difficulties that would reduce fluency along with phonemic paraphasias; she was able to repeat short but not long phrases. Grammar and single word comprehension were normal. Otherwise normal exam. MoCA was 27 (naming, repetition).

Case Study 2: MRI

Brain MRI demonstrated widening of the left Sylvian fissure due to posterior lateral temporal atrophy with preserved medial temporal lobe structure.



Case Study 2 (continued)

- **Neuropsychological testing** demonstrated mild verbal encoding impairment (5 percentile) but normal retention and retrieval with normal visual memory performance, and mildly impaired naming and verbal fluency (5 percentile); normal performance on executive function tasks and tests of other cognitive domains.
- A diagnosis was made of mild cognitive impairment, single domain language-predominant syndrome consistent with the logopenic variant of Primary Progressive Aphasia, which is often but not always due to AD

Case Study 2 – Question 1

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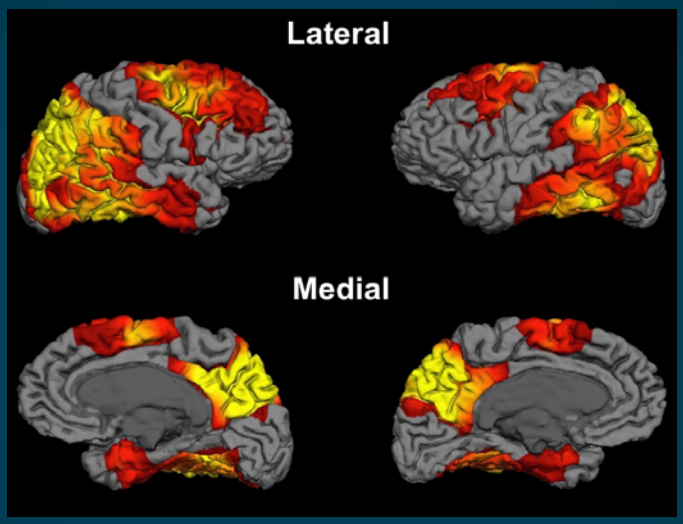
avia

A. Which of these tests would you consider at this point in your clinic?
   A. CSF analysis
   B. FDG-PET
   C. Amyloid PET
   D. A+B
   E. B+C
   F. A+C
   G. Other

Case Study 2

- FDG-PET showed left > right posterior superior temporal and inferior parietal hypometabolism with mild posterior cingulate hypometabolism.
- CSF was obtained which showed a profile of Aβ and tau proteins highly consistent with underlying AD pathology.
- As part of a research protocol, an amyloid PET scan was obtained and visually read as positive.
- These biomarkers brought diagnostic confidence to 99% confidence that the underlying disease was likely AD. The final clinical diagnosis was:
  MCI, lvPPA syndrome, highly likely due to AD pathology.

^{18}F AV-1451 Tau PET



In a patient with typical mild AD dementia, ^{18}F AV-1451 Tau PET signal is relatively symmetric in association cortices

Xia C, et al *JAMA Neurol*. 2017 Feb 20. doi: 10.1001/jamaneurol.2016.5755. [Epub ahead of print]

What We Know…

Amyloid on PET is:

- Influenced by age and APOE gene (older age and APOE-ε4 genotype are associated with higher frequency of elevated amyloid PET signal)
- Associated with:
  - Fibrillar amyloid on pathology
  - Increased rate of brain atrophy
  - Reduced glucose metabolism
  - Faster progression from MCI to dementia

BUT—not all individuals with positive amyloid PET will develop significant clinical symptoms.

Amyloid PET in the Clinic

Bradford C. Dickerson, MD

Amyloid Imaging Taskforce: Use Criteria

APPROPRIATE

1. A cognitive complaint with objectively confirmed impairment
2. Performed only after full standard workup is completed
3. AD is a possible diagnosis, but it is uncertain.
4. Knowledge of Aβ pathology would increase diagnostic certainty and alter management.
5. Should only be ordered by experts in dementia

INAPPROPRIATE

1. Used for evaluation of individuals without cognitive complaints; however, preclinical AD may become an indication for amyloid imaging if preventive treatments are proved to be effective.
2. When standard recommended clinical diagnostic testing has not been ordered for initial assessment
3. As a stand-alone diagnostic for AD dementia
4. To assess disease progression.

Johnson KA et al. *Alzheimer's Dement*. 2013 Jan;9:e1-e16. Johnson KA et al. *J Nucl Med*. 2013;54:1011-1013.

Does Amyloid-PET Impact Patient Management?

The IDEAS (Imaging Dementia—Evidence for Amyloid Scanning) study is currently recruiting:

- **Patients:** 18,488 Medicare beneficiaries meeting the criteria for appropriate amyloid-PET screening*
- **Goal**: Assess impact of amyloid PET on short-term patient management and on outcomes at 12 months versus matched controls

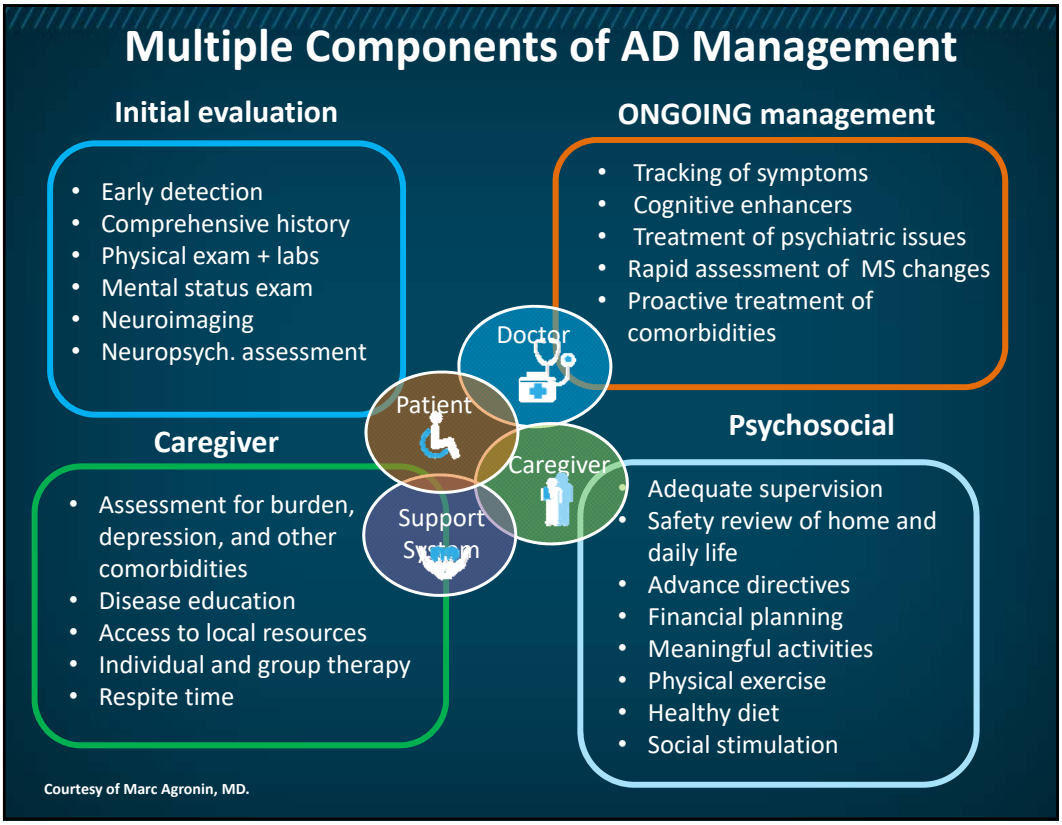
*Patients with clear, measurable cognitive deficits when there is substantial diagnostic uncertainty after a comprehensive evaluation by a dementia specialist.

NCT02420756 (https://clinicaltrials.gov/ct2/show/NCT02420756?term=NCT02420756&rank=1). www.ideas-study.org

Treatment Approaches

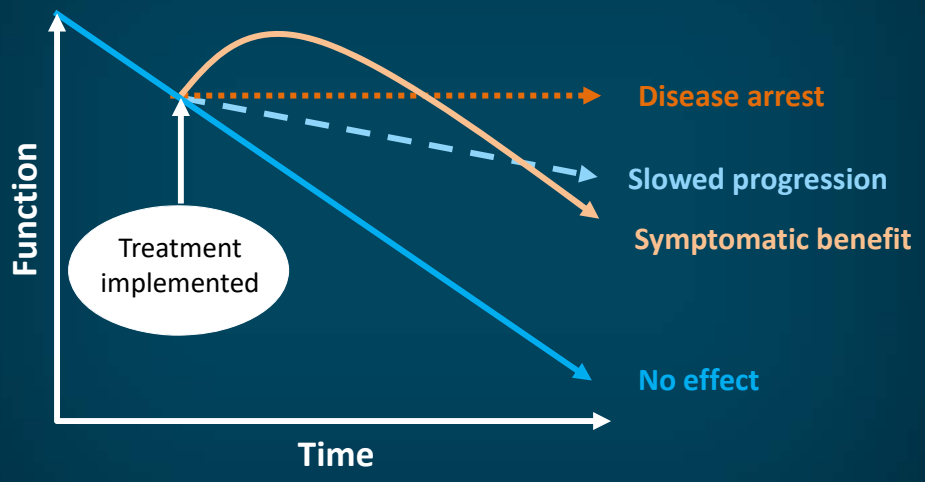
Marc Agronin, MD

Multiple Components of AD Management



Courtesy of Marc Agronin, MD.

What Are the Main Goals of Treatment?



AD Treatment Domains

Symptom improvement

- FDA-approved
  - Acetylcholinesterase inhibitors
  - NMDA-receptor antagonist
- Experimental
  - Multiple clinical trials underway

Disease modification

- No FDA-approved medications, but clinical trials are in progress on a variety of mechanisms
  - Neuronal protection
  - Protein synthesis or aggregation inhibition
  - Immunologic priming with antibodies
  - Vaccines
  - Secretase inhibition

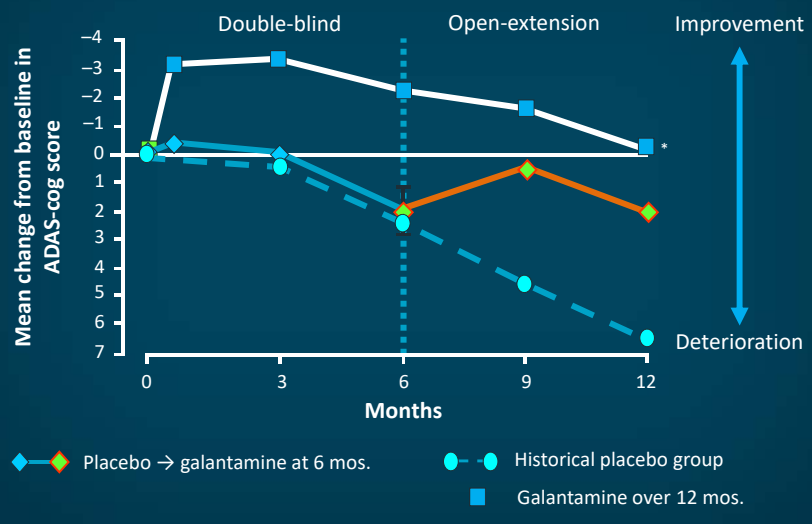
NMDA = N-methyl-D-aspartate.

Dosing for AChEIs and Memantine

Medication	Starting Dose	Dosing Range
Donepezil	5 mg/day for 4–6 weeks	5–15 mg/day; after 3 months, consider **23 mg** dose
Rivastigmine	1.5 mg BID, increasing by 1.5 mg every 2 weeks	6–12 mg/day
Rivastigmine patch	4.6 mg/day for 4 weeks	9.5 mg/day; if worsening, consider **13.3 mg** maximum dose
Galantamine	4 mg BID (8 mg once daily for XR) for 4 weeks	8–24 mg/day
Memantine (immediate release)	5 mg/day, increasing by 5 mg every week	10–20 mg/day
Memantine extended release (XR)	7 mg/day, increasing by 7 mg every week	14–28 mg/day
Memantine XR/donepezil capsule (FDC)	7 - 28 mg memantine/10 mg donepezil once daily	7-28 memantine/10 mg donepezil once daily

Donepezil prescribing information (http://labeling.pfizer.com/ShowLabeling.aspx?id=510). Rivastigmine prescribing information (www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf). Rivastigmine transdermal system prescribing information (www.pharma.us.novartis.com/product/pi/pdf/exelon.pdf). Galantamine prescribing information (www.janssenmd.com/pdf/razadyne/PI-Razadyne-RazadyneER.pdf). Memantine prescribing information (http://pi.actavis.com/data_stream.asp?product_group=1901&p=pi&language=E). Memantine extended-release prescribing information (http://pi.actavis.com/data_stream.asp?product_group=1902&p=pi&language=E). Namzaric™, Prescribing information (http://www.allergan.com/assets/pdf/namzaric_pi).

A Model of Cognitive Benefit: Galantamine (AchEI)



AChEI = acetylcholinesterase inhibitor

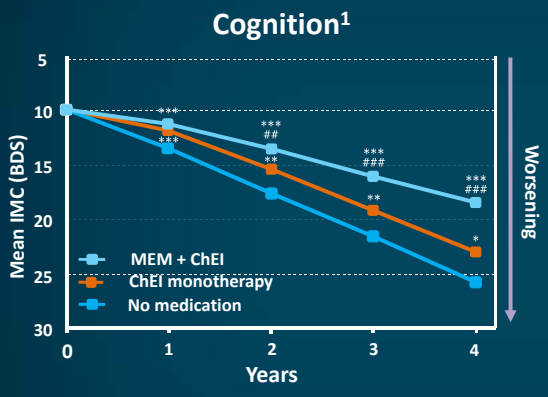
Adapted from Raskind MA et al. *Neurology*. 2000;54:2261-2268.

Common Side Effects Associated With Available Therapies for AD

Cholinesterase Inhibitors	Memantine
Nausea/vomiting	Confusion
Diarrhea	Sedation
Loss of appetite	Constipation
Dizziness	
Syncope	
Leg cramps	
Ulcers	
Cardiac arrhythmias	

Birks J. Cochrane Database Syst Rev. 2006;1:CD005593. Emre M et al. *J Alzheimer's Dis*. 2008;14:193-199. Homma A et al. *Dement Geriatr Cogn Disord*. 2008;25:399-407.

Combination Therapy vs Monotherapy in AD



- **The European Academy of Neurology Guidelines (2015) recommend combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD.[2]**
- This recommendation was based on pooled data from four long-term trials (N=1549) demonstrated significant benefits of this combination therapy vs.monotherapy.[2]
- Addition of memantine XR to a stable dose of ChEI results in significant benefits in cognition and global functioning.[3,4]

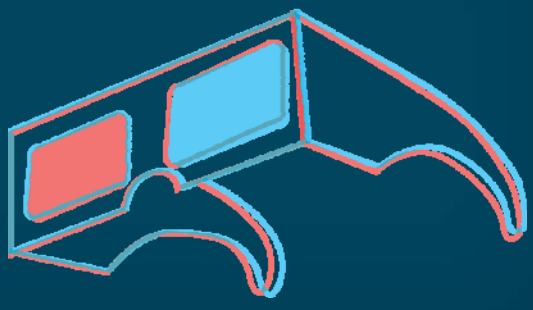
*p<0.05, **p<0.01, ***p<0.001 versus no medication;
#p<0.01, ###p<0.001 versus ChEI monotherapy

MEM= memantine; ChEI=acetylcholinesterase inhibitor; IMC= Information-Memory-Concentration; BDS (Blessed Dementia Scale).

1. Atri A, et al. Alzheimer *Dis Assoc Disord* 2008; 22: 209–221. 2. Schmidt R, et al. *Eur J Neurol*. 2015 Jun;22:889-98. Deardorff WJ, et al. *Drug Des Devel Ther.* 2016;10:3267-3279.

Disease-Modifying Therapies

Please put on your 3D glasses

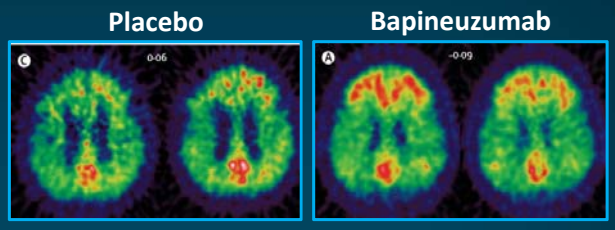


3D Video:
MOA of Disease-Modifying Therapies in AD

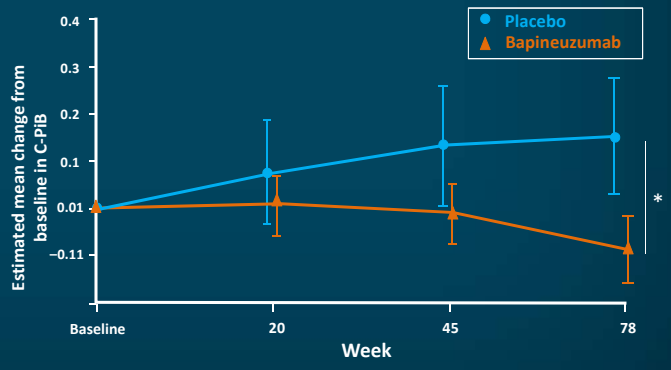
Amyloid Imaging in Clinical Trials

- All phase 3 and most phase 2b trials of anti-amyloid therapy now incorporate amyloid imaging as a study endpoint and/or for enrollment stratification.
- Prevention trials are now incorporating amyloid imaging as a trial endpoint or for enrollment stratification.
  - Amyloid imaging may be particularly important in preclinical trials to identify target cohorts for anti-amyloid therapies.

Bapineuzumab Clears Plaques in AD



Trial failed to show clinical benefit. About 17% of cohort were found not to have amyloid in the brain.

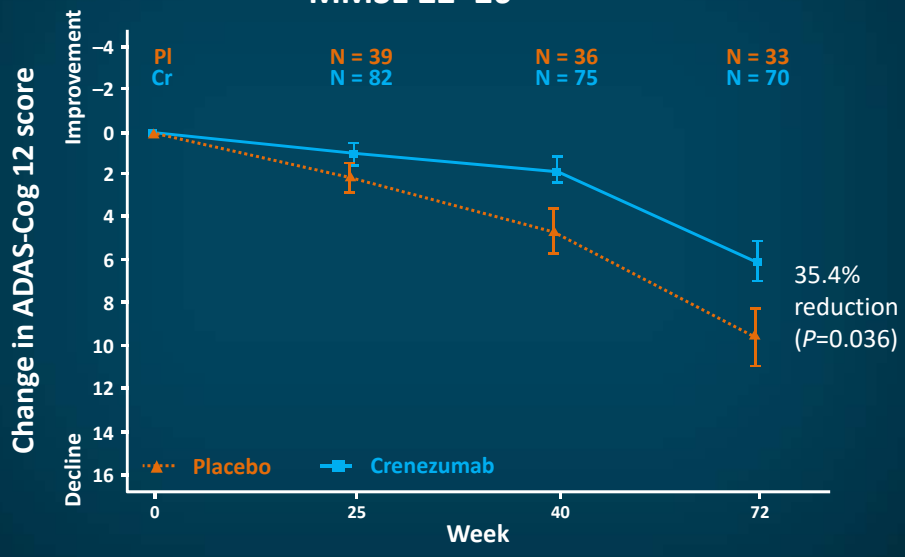


*Difference between patients in the placebo group and those in the bapineuzumab group at week 78 = –0.24 (*P*=0.003).
C-PiB = carbon-11-labeled Pittsburgh compound B.

Rinne JO et al. *Lancet Neurol.* 2010;9:363-372. Salloway S et al. *N Engl J Med.* 2014;370:322-333.

Crenezumab: Phase 2 Study in Mild-to-Moderate AD

MMSE 22–26



Cummings J et al. *Alzheimer's Dement.* 2014;10(4 suppl):P275(abstract O4-11-06).

Solanezumab Clinical Trials

- **EXPEDITION, EXPEDITION 2[1]**
  - N = 1322; trials in mild-to-moderate dementia
  - About 25% did not have amyloid in the brain at baseline.
  - There was **a 34% reduction in clinical decline in mild dementia but no effect in moderate dementia**
- **EXPEDITION 3[2]**
  - Mild AD (N =2129)
    - Probable AD by NINCDS/ADRDA criteria
    - Amyloid positive by F^{18} florbetapir PET or CSF $A\beta_{1-42}$
    - MMSE score 20-26 inclusive
    - Primary endpoint: change in cognition ($ADAS\text{-}Cog_{14}$)
    - On stable standard of care therapy (drug and non-drug)

ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; MMSE=mini-Mental State Examination

1. Doody RS et al. *N Engl J Med.* 2014;370:311-321. 2. NCT01900665.

EXPEDITION 3: Solanezumab Initiated in Mild AD

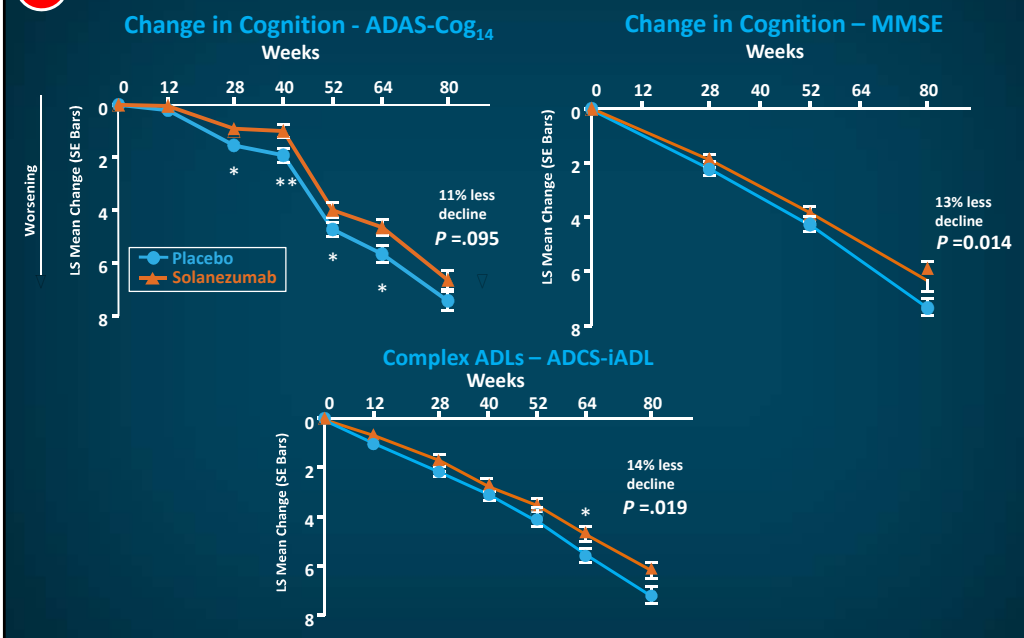
Baseline Demographics

Demographic	Placebo (N=1072)	Solanezumab (N=1057)	P-value
Age, years, mean (SD)	73.3 (8.0)	72.7 (7.8)	0.073
Female, n (%)	631 (58.9%)	600 (56.8%)	0.335
Race, n (%)			0.758
White	894 (90.7%)	878 (90.5%)	
Black or African American	19 (1.9%)	14 (1.4%)	
Asian	71 (7.2%)	75 (7.7%)	
APOE ε4 carriers, n (%)	685 (66.3%)	712 (69.3%)	0.144
Education, years, mean (SD)	13.7 (3.8)	13.7 (3.7)	0.906
Symptom onset, years, mean (SD)	4.3 (2.6)	4.2 (2.5)	0.413
Diagnosis, years, mean (SD)	1.6 (1.7)	1.5 (1.6)	0.132
AChEI and/or memantine use, n (%)	856 (79.9%)	822 (77.8%)	0.244

*Based on number of patients with available APOE status (placebo N=1033); solanezumab N=1027).

Adapted from Honing L. Presentation, CTAD 2016.

EXPEDITION3: Solanezumab Initiated in Mild AD



*P≤0.05;**P≤0.01.

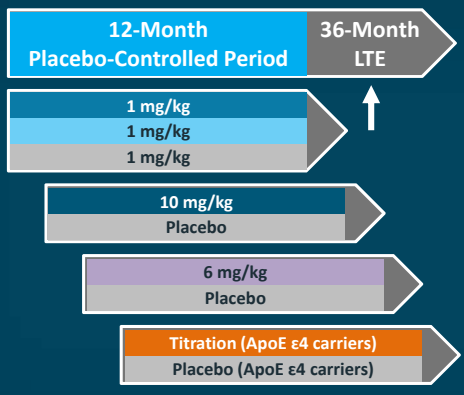
Adapted from Honing L. Presentation, CTAD 2016.

Aducanumab Phase 1 Study (PRIME)

Staggered Parallel-Group Design

Population

- **Prodromal or mild AD**
- MMSE ≥20
- Stable concomitant medications
- Positive amyloid PET scan



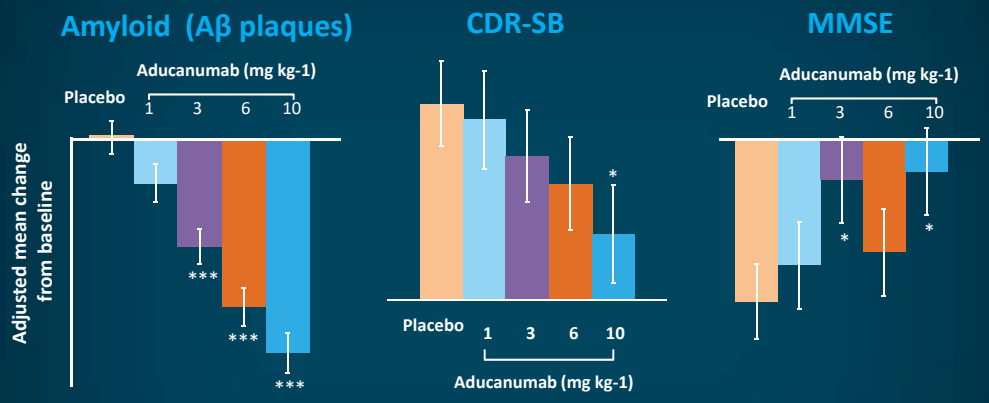
Endpoints

- **Primary endpoint:** safety and tolerability
- **Secondary endpoints:** serum PK, immunogenicity, change in amyloid PET (Week 26)
- **Exploratory endpoints** included CDR-SB, MMSE, change in amyloid PET (Week 54)

- **Randomization**: 3:1 active: placebo with cohorts, fixed-dose cohorts stratified by ApoE ε4 status
- **Planned sample size**: 188 patients
- **Titration cohort** of ApoE e4 carriers added after enrollment into fixed-dose arms was complete (planned sample size 21 aducanumab: 7 placebo)

CDR-SB, Clinical Dementia Rating-Sum of Boxes; LTE, long-term extension; MMSE, Mini-Mental State Examination; PET, positron emission tomography.

Aducanumab Phase 1 Study: Results at 54 Weeks (Fixed dose)



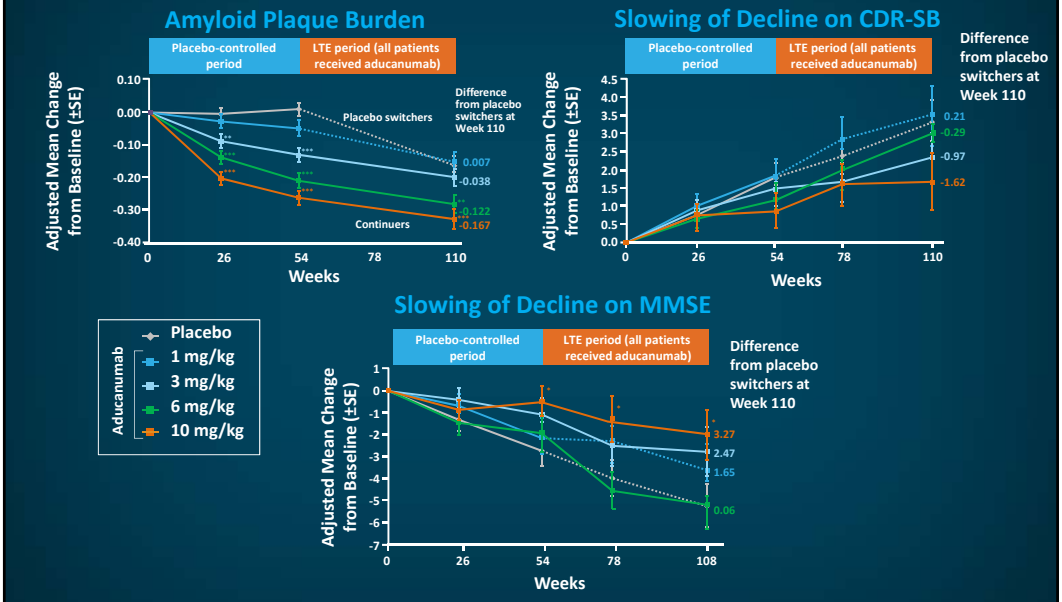
*P < 0.05, **P < 0.01,***P < 0.001 versus placebo

The most common adverse effects with aducanumab were amyloid-related imaging abnormalities (ARIA), headache, urinary tract infection, and upper respiratory tract infection. The only serious adverse effects with aducanumab were **ARIA (3-16% at 1-10mg/kg)** and CNS superficial siderosis.

CDR-SB = Clinical Dementia Rating—Sum of Boxes; MMSE = Mini Mental State Examination.

Sevigny J et al. *Nature*. 2016;537(7618):50-6.

Aducanumab PRIME: Clinical Endpoints at 24 Months (Fixed dose)



*Nominal P<0.05 (vs placebo [Week 52] of placebo switchers (Weeks 76 and 108).

**Nominal P<0.01; ***Nominal P<0.001 vs placebo in the placebo-controlled period and vs placebo switchers in the LIE period.

Iterim Analysis, adapted from Viglietta A Presentation, CTAD, December 9, 2016.

Amyloid-related Imaging Abnormalities (ARIAs)

- White-matter lesions with or without evidence of brain edema obtained by neuroimaging
  - ARIA-E: fluid-attenuated inversion recovery (FLAIR) MRI due to vasogenic edema
  - ARIA-H: MRI abnormalities due to microhemorrhages and hemosiderosis
- They typically resolve
- Their presence is not always associated with symptoms
- Primarily a function of *ApoE* and higher doses of anti-amyloid antibodies

Sperling RA et al. *Alzheimer's Dement*. 2011;7:367-385. Sperling R et al. *Lancet Neurol.* 2012;11:241-249.

Aducanumab PRIME Study: Safety (Titration Cohort)

	Placebo	Aducanumab				
		1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg	Titration
Patients with at least 1 post-baseline MRI	46	31	32	30	32	23
ARIA-E,[a] n (%)	0/46	1/31 **(3)**	2/32 **(6)**	11/30 **(37)**	13/32 **(41)**	8/23 **(35)**
ApoE ε4 carrier	0/32	1/19 **(5)**	1/21 **(5)**	9/21 **(43)**	11/20 **(55)**	8/23 **(35)**
ApoE ε4 non-carrier	0/14	0/12	1/11 **(9)**	2/9 **(22)**	2/12 **(17)**	—
Isolated ARIA-H, n (%)	3/46 (7)	2/31 (6)	3/32 (9)	0/30	2/32 (6)	0/23

[a]ARIA-E with or without ARIA-H.

- Majority of ARIA-E within first 5 months of treatment
- 75% asymptomatic
- 2 patients (25%) had mild symptoms that resolved
- MRI findings resolved within 4-12 weeks

ARIA-E, ARIA-vasogenic edema; ARIA-H, ARIA-microhemorrhages, macrohemorrhages, or superficial siderosis; MRI, magnetic resonance imaging.

Adapted from Viglietta A Presentation, CTAD, December 9, 2016.

Added last row

RCTs in Presymptomatic AD

RCT	ADCS-A4[1]	API[2]	DIAN[3]	TOMORROW[4]
Population and sample size	Older adults without cognitive impairment (N = 1150)	Early onset familiar AD (Columbia +US) (N = 300)	Early-onset familial AD, no symptomatic or mild cognitive impairment (N = 240)	Older adults at risk of developing MCI due to AD within 5 years. (algorithm including age and *TOMM40* and *APOE*) (N=5000)
Inclusion criteria	Amyloid PET positive	Carrier *PSEN1* vs. non carriers	Carrier of *PSEN1*, *PSEN2*, *APP* (N=120) (vs. non carriers)	High risk based on algorithm including age and *TOMM40* and *APOE*
Age (years)	65–85	30–60	18–80	68-83
Intervention	**solanezumab**	**crenezumab**	**gantenerumab or solanezumab**	**pioglitazone**
Duration	3 years + 2 years ext.	5 years	2 years + 3 years ext.	5 years
Outcomes	1ary: cognitive function 2ary: change in AD biomarkers	1ary: cognitive function 2ary: change in AD biomarkers	1ary: change in AD biomarkers	1ary: cognitive function 2ary: qualification of algorithm based on *TOMM40* and *APOE*

Adapted from Solomon A et al. *J Intern Med*. 2014;275:229-250. 1. NCT02228357. 2. NCT01998841 3. www.nia.nih.gov/alzheimers/clinical-trials/dominantly-inherited-alzheimer-network-trial-opportunity-prevent-dementia. 4. NCT02284906.

I have Changed the bullet after CTAD

Lessons from Anti-amyloid Antibody Trials

- Crenezumab study suggests therapeutic effects were larger in mild-stage than in moderate-stage AD.
- Solanezumab most recent data have not shown a significant slowing of disease progression in mild AD.
- Aducanumab studies suggests dose adjustments in ApoE ε4 carriers with greater risk of ARIAs to maximize potential for therapeutic benefits and support ongoing Phase 3 studies
- Increasingly, immunotherapy trials are looking to intervene at earlier stages to see if disease progression can be interrupted prior to symptomatic onset.

Other Experimental Agents

Mechanism	Agent	Stage
β-secretase inhibition	Verubecestat (MK-8931) LY3314814 JNJ-54861911 E2609	FAILED Phase 3 Phase 2/3 Phase 3
γ-secretase inhibition	Semagacestat Avagacestat	FAILED FAILED
γ-secretase modulation	Tarenflurbil	FAILED
Fibrillogenesis inhibition	Tramiprosate	FAILED
5HT6 antagonism	Intepirdine, Idalopirdine	Phase 3 FAILED
RAGE antagonism	Azeliragon	Phase 3
Melatonin receptor antagonism	Piromelatine	Phase 2
Protein kinase C activator	Bryostatin	FAILED

Available at http://www.alzforum.org/therapeutics. Accessed on March 5, 2016.

Tau Based Approaches

Mechanism	Agent	Stage
Tau aggregation inhibition	TRx0237 (stabilized, reduced form of methylthionine /Methylene Blue)[1]	FAILED
Anti-tau antibodies	ABBV-8E12 and others	Phase 1 and 2 trials ongoing
Protein kinase inhibition	Lithium studied as an inhibitor of glycogen synthase kinase 3 (GSK3)	FAILED
Anti-tau vaccine	AADvac1[2]	Phase 2

1. Gautier S, et al. *Lancet*. 2016; 388: 2873–2884. 2. Novak et al. *Lancet Neurology* 2016; 16:123-134.

Miscellaneous Meds for AD

AGENT	NOTES
Curcumin	Theorized anti-oxidant, anti-tumor, anti-inflammatory and other mechanisms. Blocked beta-amyloid accumulation in transgenic mice. Does not appear to penetrate blood brain barrier
Statins	Initial study suggested AD risk reduction, possibly through direct effects on beta-amyloid. No cognitive benefit found in AD[1]
Vitamin E	No benefit in reducing conversion rate of MCI to AD. High dose (2000 IU) in combination with acetycholinesterase inhibitors (nut not memantine) showed modest functional benefit over placebo[2,3]
Gingko biloba	Did not prevent onset of AD. No clear cognitive benefits established
DHA (fish oil)	Source of omega-3 fatty acids, did not benefit AD patients
Resveratrol	Antioxidant found to lower beta-amyloid in cultured cells, but no evidence established for actual AD risk reduction
Cerefolin NAC Vayacog	Medical foods in pill forms. Cerefolin contains folate, B_{12}, and N-acetylcycsteine. Vayacog contains omega-3 fatty acids + phosphotidyl serine. No proven benefit for AD
Axona	Medical food in powder form: limited evidence suggests improved cognition in mild to moderate AD patients who are APOE4 negative[4] Initial results from large-scale trial were negative.

1. McGuinness B, et al. *Cochrane Database Syst Rev*. 2016 Jan 4;(1):CD003160. 2. Dysken MW , et al. *JAMA*. 2014;311:33-44. 3. Petersen RC, et al. *N Engl J Med*. 2005;352:2379-88. 4. Henderson ST, et al. *Nutr Metab* (Lond). 2009 Aug 10;6:31.

Case Study: James

- James is a 78 year old married man who was diagnosed with early stage Alzheimer's disease.
- He has a MMSE score of 24/30
- His MRI showed mild small vessel ischemic disease. His amyloid PET scan was positive
- He has hyperlipidemia, hypertension and obstructive sleep apnea, but is generally considered medically stable
- He has no psychiatric diagnoses other than AD
- He has been started on donepezil and currently takes 10 mg
- His wife Patricia wants to know: what else should they be doing?

Case Study: James - Question 1

What would you recommend to James and Patricia?

A. Add memantine
B. Add sertraline
C. Enroll in a day program
D. Consider enrolling in a clinical trial
E. Add Vitamin E and curcumin supplements

Case Study: James - Question 2

James and Patricia were interested in a clinical trial for Alzheimer's disease, but didn't know where to start. What would you recommend?

A. Google search for local memory centers
B. Facebook ads
C. www.alz.org
D. Alzheimer's Association TrialMatch
E. www.Clinicaltrials.gov
F. All of the above

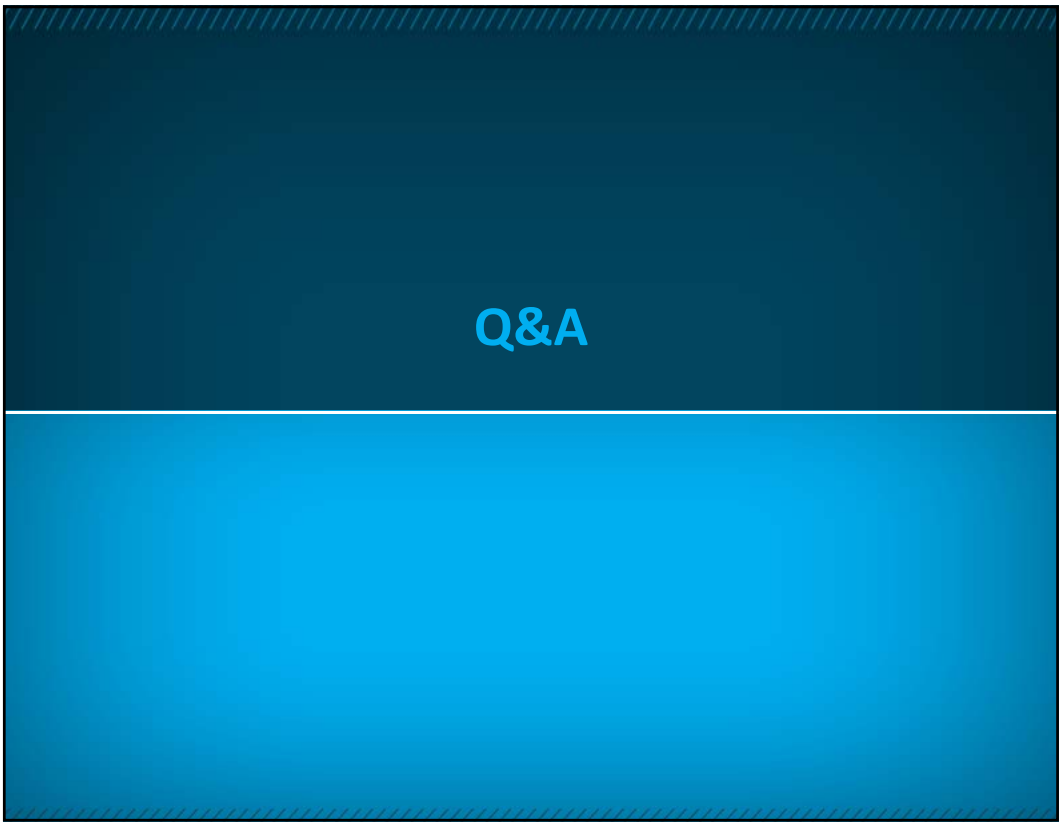
Case Study: James- Question 3

James and Patricia found a center and are considering a clinical trial. Which of the following would be important for them to know?

A. Clinical trials are free and may pay a stipend
B. Once you agree to a trial, you are committed until it ends
C. Most trials have a placebo arm
D. There is no need for a study partner
E. A and C
F. None of the above

Clinical Pearls

- Comprehensive assessment of patients with suspected prodromal or atypical AD often benefits from the use of newer diagnostic biomarkers, including FDG PET, amyloid PET, or spinal fluid examination.
- Amyloid imaging is now available in the clinic; indications and guidelines for use have been defined. Studies are in progress to evaluate its utility.
- Tau imaging is in development.
- Several agents with different mechanisms of action are in clinical trials to evaluate whether disease progression can be slowed.


Q&A